B-cell Epitopes on the Envelope Glycoproteins of SIV and HIV-2

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Introduction

SIV, HIV-2 and HIV-1 are all members of the lentivirus subfamily of retroviruses. These viruses all share similar genomic organization and biological properties but are distinguishable antigenically. HIV-1 and HIV-2 share only 55–60% amino acid homology in the pol gene product whereas HIV-2 and SIV strains (excluding SIVagm) share 84–92% homology (Desrosiers et al. 1989; Chen et al. 1996). SIV AGM forms a distinct group of its own and has 55–60% homology with both the HIV-1 and the SIV/HIV-2 groups. African green monkeys and sooty mangabeys are naturally infected with strains of SIV and there is no evidence to suggest that these infections cause disease (Kanki et al. 1986; Murphey-Corb et al. 1986). In contrast, SIV infection of macaques (Daniel et al. 1985; McClure et al. 1989) resulting from accidental or experimental infection with SIV isolates from sooty mangabeys gives rise to typical symptoms of AIDS in the infected animals (Letvin et al. 1985, 1990). Several strains of SIV have been recognized and these are named after the species from which they were isolated e.g. SIVmac from macaques, SIVsmm from sooty mangabey, SIVagm from African green monkey, SIVmnd from mandrills (Desrosiers, 1988) and SIVmne from pig-tailed macaques (Hu et al. 1992).

Genetic analyses suggest that HIV-2 arose in West Africa as the consequence of a sooty mangabey-human cross-species transmission (Desrosiers et al. 1989; Chen et al. 1996) and HIV-2 was first isolated from a patient from West Africa (Clavel et al. 1986; Kanki et al. 1987; Albert et al. 1987). The geographic distribution of HIV-2 remains largely confined to West Africa and countries with social or economic links with this region although HIV-2 infection in Africa, Europe, the Americas and Asia, with a particularly high prevalence in India (Dietrich et. al, 1995), has also been documented. HIV-2 strains are less pathogenic than their HIV-1 counterparts and HIV-2 infected patients show milder symptoms, if any, and survive longer than patients infected with HIV-1 although infection does eventually lead to AIDS (Marlink, 1996). HIV-2 has been divided into 5 different subtypes, A to E, with the most common subtypes being A and B.

Purpose of the review

In this review article we have summarized the B-cell epitopes on SIV and HIV-2 envelope glycoproteins that have been mapped with monoclonal antibodies or with polyclonal antisera. For clarity, the epitopes of SIV and HIV-2 have been described separately and for each virus the epitopes are described in order from the amino terminus to the carboxyl terminus of the envelope precursor. Where appropriate, reference is made in the text to those epitopes which are common to both viruses, and a more detailed discussion of the similarities and differences between the two viruses is given in the Discussion section at the end. Tables 1 and 2 provide a comprehensive list of mapped epitopes on the envelope glycoproteins of SIV and HIV-2 respectively, together with the identity and source of the antibodies used to define them. For the SIV envelope epitopes described, epitope mapping was based on two series of overlapping 20-mer peptides, EVA 774.1–774.9 for gp120, and EVA 798.1–798.36 for gp41. Both of these series are available from the repository for the EC Programme, EVA. The sequence used is the consensus sequence of SIVmac 32H evelope protein, described in Almond et. al., 1992, accession numbers 74936 and 74958.

B-cell epitopes on SIV envelope glycoproteins

Comparisons of nucleotide sequences of the envelope genes of SIV and HIV have identified discrete variable regions interspersed with less variable or constant regions (Burns and Desrosiers, 1991). For SIVmac, the variable regions V1, V2, V4 and V5 correspond to the analogous regions on the HIV-1 envelope gene. However, an immunogenic cysteine loop between V2 and V4 of SIV gp120 was not found to be antigenically variable but for the purposes of the review this region will be referred to as the SIV V3 region. A more variable region, carboxyl-terminal to the cysteine loop, between aa371–377, has been described (Burns and Desrosiers, 1991).

C1

Three linear epitopes in the C1 region of SIV gp120 have been identified using murine MAbs (Kent et al. 1993; Collignon, personal communication). Two of the epitopes defined by peptides aa21–40 (KK3, KK18, Senv71.1) and aa41–60 (KK68) are SIV specific whereas the epitope defined by aa81–100 is common to strains of SIV and HIV-2 (Kent et al. 1991; Mannervik et al. 1992). The linear epitope at aa41–60 is also recognized by sera from macaques infected with the J5 molecular clone of SIVmac32H (McBride et al. 1993).

V1

In three separate studies a linear epitope at aa111–130 within the V1 region was shown to be recognized by sera from infected macaques (Benichou et al. 1993; McBride et al. 1993; Silvera et al. 1994) and in one of these studies (Silvera et al. 1994) an adjacent epitope at aa141–160 was also recognized. Three SIVmac specific monoclonal antibodies KK65, KK66 and KK67 mapping to the linear sequence at aa141–160 have been generated (Kent et al. 1992) but none of these antibodies have any known biological activity. These studies highlight the antigenic nature of the V1 region and the specificity of the MAbs for strains of SIV emphasizes the variable nature of this region.

V1/V2

A number of murine MAbs mapping to aa8–303 spanning the V1/V2 region have been described (Kent et al. 1991, 1992; Collignon, personal communication). These antibodies (eg. KK8 and Senv50.1) react in Western blot, bind to native antigen on virus infected cells, react with an amino-terminal peptide of approximately 300 amino acids but fail to react with any linear 20-mer peptides, thus suggesting that the conformation of the epitope may be important for antibody binding.

V2

Neutralizing and non-neutralizing monoclonal antibodies (MAbs) mapping to the V2 region of gp120 have been generated in a number of studies (Collignon, personal communication; Benichou et al. 1992; Kent et al. 1991; Kent et al. 1992; Matsumi et al. 1995). Two MAbs, SKB 1.1 and MATG2033, map to an epitope spanning aa161–180 (Benichou et al. 1992; Collignon, personal communication). A further seven antibodies have been described which map to an adjacent linear epitope spanning aa171–190 in the V2 region (Kent et al. 1992; Benichou et al. 1992; Matsumi et al. 1995): five of these antibodies have neutralizing activity (Kent et al. 1992; Benichou et al. 1992; Matsumi et al. 1995). Further analysis of the neutralizing and non-neutralizing antibodies with a panel of six overlapping 18-mer peptides (ADP795 peptides 1–6) showed that each antibody had a distinct pattern of reactivity. Hence, antibodies to multiple epitopes within this region are able to neutralize infectivity (Kent et al. 1993). Most of the V2 antibodies described to date react only with strains of SIV, although the neutralizing antibody M318T (Matsumi et al. 1995) and the non-neutralizing antibody KK52 (Kent et al. 1992) are able to cross-react with strains of HIV-2 in binding assays. The immunogenic nature of the V2 epitope has been confirmed in peptide binding studies using sera from SIVmac (McBride et al. 1993; Silvera et al. 1994; Torres et al. 1993a; Benichou et al. 1993) and SIVsm (Samuelsson et al. 1993) infected macaques and in all of these studies reactivity with peptides spanning aa161–190 and 170–196 for SIVmac and SIVsm respectively has been described.

C2/V3

Two epitopes within the C2 and C2/V3 region are immunogenic in infected macaques. McBride et al. (1993) found that sera from macaques infected with SIVmac J5 bound to a peptide spanning aa221–240 and in a study by Torres et al. (1993a), sera from macaques infected with SIVmac251 recognized aa294–305.

V3

Studies of sera from SIVmac infected macaques have demonstrated binding of antibody to linear epitopes at aa311–340 within the cysteine loop (Benichou et al. 1993, McBride et al. 1993, Silvera et al. 1994) and at aa331–350 at the carboxyl terminal end of the same region (Silvera et al. 1994). Similarly, the sera from macaques infected with SIVsm recognize a peptide spanning aa313–346 (Samuelsson et al. 1993). Naturally infected African green monkeys also make an antibody response to the V3 region of SIVagm spanning aa317–350 (Siegel et al. 1992). However, the V3 region is reported not to elicit a strong neutralizing response in macaques (Javaherian et al. 1992).

Three monoclonal antibodies mapping to the V3 cysteine loop of SIVmac have been generated but these failed to neutralize the infectivity of SIVmac (Kent et al 1992). SIVagm is not neutralisable by immune serum but a monoclonal antibody AG1.0, recognizing the V3 region of SIVagm, neutralized the TYO strain, but only in the presence of soluble CD4 (Allan, personal communication).

V4

A predicted immunogenic peptide spanning the region aa414–434, when conjugated to KLH, BSA or cross-linked with glutaraldehyde, generated neutralizing antibody in mice (Torres et al. 1993b). Similar epitopes in the V4 region (aa414–434 and aa421–440) are recognized by sera from infected macaques (Torres et al. 1993a, 1993b, Silvera et al. 1994). Two monoclonal antibodies, one of which was shown to have syncytium inhibiting and neutralizing activity also mapped to the V4 region recognizing a linear epitope at aa411–430 (Babas et al. 1995).

C4

The generation of monoclonal antibodies mapping to the CD4 binding site has not been described and similarly, sera from infected macaques are not reported to bind to any peptides spanning this region. However, four monoclonal antibodies are reported to inhibit the binding of SIV gp120 to sCD4 (Doyle et al. 1995). MAbs KK3 and KK18 map to amino acids 21–40 in the C1 region (see above) at the N-terminal end of gp120 (Kent et al. 1992) whereas KK44 and KK56 recognize conformation-dependent epitopes (see below). These two groups of antibodies do not cross-compete and only the latter pair of antibodies show neutralizing activity (Kent et al. 1993).

C5

Binding of sera from infected macaques to a peptide spanning aa501–520 has been reported for SIVmac (McBride et al. 1993, Silvera et al. 1994), aa514–537 for SIVsm (Samuelsson et al. 1993) and aa525–537 for SIVagm (Siegel et al. 1992) but monoclonal antibodies binding to this highly conserved region have not been described.

Conformation dependent epitopes

A murine monoclonal antibody recognizing a conformation-dependent epitope on the external envelope glycoprotein of SIVmac251 was generated but this antibody failed to neutralize virus infectivity (Babas et al. 1995). In contrast, a group of cross-competing antibodies which shows potent neutralizing activity was identified in two independent studies (Collignon, personal communication; Kent et al. 1991, Kent et al. 1992). This group of antibodies reacts well in immunoprecipitation assays and recognizes native envelope on the surface of virus infected cells, but does not react in Western blot and have not been mapped with envelope fragments or with overlapping 20-mer peptides. Cross-competition studies suggest that this group of antibodies recognize related but distinguishable conformation-dependent

epitopes (Kent et al. 1993). In a study by Javaherian et al. (1994), MAbs KK5 and KK9 were shown to bind to a 45kDa C-terminal fragment of gp120 which included the V3, V4 and V5 regions but binding was abrogated when the peptide fragment was cleaved between the V3 and V4 regions. This evidence suggested that the conformation across the V3/V4 region was critical for antibody binding. Escape mutant and deletion mutant studies were further able to define the binding sites of this group of antibodies (Kent et al. 1993, Choi et al. 1994). In studies by Kent et al. (1993) two escape mutants were generated by culturing the J5 molecular clone of SIVmac 32H (Rud et al. 1994) in the presence of the monoclonal antibody KK9. Sequence analysis of the two escape mutants identified a point mutation R to K at position 340 in the V3 region in the first mutant and a point mutation R to K at position 429 in the V4 region in the second mutant. Binding studies showed that the V3 mutation abrogated binding of KK9 only whereas the point mutation in V4 abrogated the binding of all 7 cross-competing neutralizing antibodies. Deletion mutant studies identified a point mutation N to D at position 409, deletion of 420–423KPKE and deletion of 422–425KEQH as critical for binding of this group of antibodies. Mutation of the V5 region of SIVmac239 did not alter the binding of the antibodies (Choi et al. 1994). Binding studies have shown that the antibodies recognizing conformation dependent epitopes do not cross-react with strains of HIV-2 (Kent et al. 1991, 1993). However, in competition studies using SIV gp120, this group of antibodies blocked the binding of a panel of human monoclonal antibodies (HuMAbs) derived from a patient infected with HIV-2 thus suggesting that common elements of the conformation-dependent epitope are shared by SIV and HIV-2 (Robinson, personal communication, Kent et al. 1993). Competition of neutralizing MAbs with sera from infected macaques suggests that conformation-dependent epitopes are exposed on the native virus and that these epitopes are capable of generating an immune response *in vivo* (McBride et al. 1993). Monoclonal antibodies recognizing conformation-dependent epitopes on the external envelope glycoprotein of SIVagm have also been described (Otteken et al. 1993).

SIV gp41

SIV gp41 has a highly conserved immunogenic epitope spanning aa601–620 which is recognized by murine monoclonal antibodies (Collignon, personal communication, Kent et al. 1992; Otteken et al. 1993) and by sera from experimentally or naturally infected macaques (Benichou et al. 1993; Silvera et al. 1994; Siegel et al. 1992). Sera from SIVsm infected macaques recognize a similar epitope at aa608–638 (Samuelsson et al. 1993). The MAbs recognizing this epitope cross-react with a range of SIV isolates and also with HIV-2. Two MAbs mapping to an epitope at aa591–610 adjacent to the immunodominant epitope are SIVmac specific. Another cross-reactive epitope defined with monoclonal antibodies, which cannot be mapped with linear peptides, has also been described (Kent et al. 1992; Collignon, personal communication). A neutralizing MAb has been generated which recognizes an epitope in gp41 specific for SIVmac251 (Kodama et al. 1991). Fine mapping studies identified the amino acids DWNND at position aa106–110 as critical for binding of this antibody.

Four additional linear epitopes at aa651–690, aa701–760, aa761–830 and aa831–878 are recognized by sera from infected macaques (Silvera et al. 1994).

B-cell epitopes on HIV-2 envelope glycoproteins

The genomic organization of HIV-2 envelope is very similar to that of SIV and the V1, V2, V4 and V5 regions are analogous to those of HIV-1. As with SIV, the region of HIV-2 envelope analogous to the V3 region of HIV-1 is less hypervariable, but is immunogenic *in vitro* and *in vivo*.

C1

In two recent studies, MAbs mapping to regions of C1 were generated. McKnight et,al. (1996) described a rat MAb mapping to aa44–53 whereas Traincard et al. (1994) described mouse antibodies mapping to aa48–57 and aa83–97. A linear antigenic site at aa44–56 has also been defined using sera from an HIV-2 infected patient (Norrby et al. 1991: Mannervik et al. 1992).

V1

A linear antigenic site has been identified in the V1 region using patient sera (de Wolf et al. 1991) and this region has also been implicated as the target of a rat neutralizing monoclonal antibody (McKnight et al. 1996) and of sera from guinea pigs immunized with peptides spanning the region aa119–137 (Björling et al. 1991).

V2

The V2 region of HIV-2 gp125 is an important target for antibody binding. In several recent reports, MAbs binding to the V2 region (aa140–181) were described. MAb 44.2g was able to neutralize HIV-2 and SIVsm and this antibody was also able to cross-react with, but not neutralize SIVmac, (McKnight et al. 1996). As with SIV, not all antibodies to the V2 region are able to neutralize HIV-2 infectivity. Four MAbs have been described which map to defined peptides within the V2 region, two are HIV-2 specific whereas the other two MAbs (125-I and 44.1b), were able to cross-react with SIVmac in binding assays (Traincard et al. 1994; McKnight et al. 1996). Furthermore, sera from rabbits immunized with V2 peptides were unable to inhibit syncytia formation *in vitro* (Babas et al. 1994). In studies of HIV-2 infected patients, the majority of a panel of human sera reacted with overlapping peptides spanning the central and C-terminal regions of V2 (aa160–189 and aa189–205) (Skott et al, personal communication) thus confirming the antigenic nature of this epitope *in vivo*.

C2

Three linear epitopes within the C2 region have been defined with a rat MAb (aa223–234) (McKnight et al. 1996) or with patient sera (aa196–215 and aa234–248) (Mannervik et al. 1992). The rat MAb 44.6i was able to react with diverse strains of HIV-2 but no cross-reaction with SIV was reported (McKnight et al. 1996).

V3

Using patient sera, the V3 region of HIV-2 gp125 was shown in a number of studies to be a linear antibody binding site (de Wolf et al. 1991; Norrby et al. 1991; Mannervik et al. 1992; Robert-Guroff et al. 1992). However, the role of the linear HIV-2 V3 region as a target for neutralizing antibody remains controversial. Polyclonal antisera raised by immunization with V3 peptides (Robert-Guroff et al. 1992: Babas et al. 1994) and two MAbs (32.7 and 125-F) mapping to aa306–311 and aa314–332 respectively (McKnight et al. 1996, Traincard et al. 1994) failed to show neutralizing activity. In contrast, Björling et al. (1991, 1994) have identified the V3 loop as a target for neutralizing antibody by peptide immunization, by blocking neutralization with peptides corresponding to the V3 loop (aa311–330 and aa318–337) and by generation of murine MAbs to this region. Fine mapping studies have defined two antigenic sites with conserved motifs important for antibody binding, Phe-His-Ser at position aa315–317 and Trp-Cys-Arg at aa329–331. A murine MAb mapping to a 6 amino acid segment with the core sequence His-Tyr-Gln (aa316–318) (Matsushita et al. 1995) and rat MAb mapping to aa304–311 (McKnight et al. 1996) have also been reported to show neutralizing activity. Similarly, hyperimmune sera from guinea pigs immunized with V3 peptides were shown to have broad cross-neutralizing activity including neutralization of several primary isolates of HIV-2 from Guinea Bissau (Björling et al. 1994).

C3

One linear epitope in the C3 region of HIV-2 gp125 is recognized by human patient sera (aa340–358) (de Wolf et al. 1991) while a mouse Mab mapping to an adjacent linear epitope at aa366–392 showed weak neutralizing activity (Matsushita et al. 1995).

V4

In the V4 region of HIV-2 gp125, a linear site at aa398–416 is recognized by human patient sera (Mannervik et al. 1992) but no biological function has yet been ascribed to this epitope. MAbs mapping to the region have not been described.

C4

Monoclonal antibodies binding to the C4 region have not been described, but de Wolf et al. (1991) and Norrby et al. (1991) have observed that patient sera bind weakly to linear peptides spanning the region aa436–452. Mutation studies have identified a Tryptophan residue at position 428 that may be critical for HIV-2 gp125/CD4 interaction and fusion (Keller et al. 1993) and this may be analogous to the Trp-427 residue of HIV-1 which was identified as serving a similar function (Cordonnier et al. 1989; Olshevsky et al. 1990).

Carboxyl terminus

The carboxyl-terminus of HIV-2 gp125 has an immunodominant site that reacts with the majority of sera from HIV-1 and HIV-2 infected patients (Palker et al. 1987; Norrby et al. 1991; Broliden et al. 1992). Two overlapping peptides (aa472–493 and aa489–509) have been shown to induce neutralizing activity in guinea pigs and to block some of the neutralizing activity in patient sera (Björling et al. 1991). The region spanning aa481–507 has been shown in two separate studies to be recognized by sera from patients infected with HIV-2 (de Wolf et al. 1991; Mannervik et al. 1992).

Conformation dependent epitopes

Antibodies mapping to conformation dependent epitope of HIV-2 have been generated. Three rat MAbs were generated following immunization with baculovirus derived gp105 and one of these antibodies (28.8e) was able to neutralize potently HIV-2 infectivity (McKnight et al. 1996). Neutralizing human MAbs derived from an HIV-2 infected patient were shown in binding studies to cross-react with a range of SIV and HIV-2 antigens and were able to compete with SIV antibodies for binding to SIV antigen (Robinson, personal communication; Kent et al. 1993).

HIV-2 gp36

The highly immunodominant region of HIV-2 gp36 analogous to that of SIV is recognized by sera from HIV-2 infected patients (Norrby et al. 1991). A neutralizing epitope in the amino terminal region of HIV-2 gp36 has been identified by peptide immunization of guinea pigs (Skott, personal communication) and this corresponds to the location of an equivalent epitope in HIV-1 gp41 (Chanh et al. 1986; Ho et al. 1987). Three MAbs mapping to the region aa578–603 have been described and one of these (36-C is cross-reactive with SIV (Traincard et al. 1994) Furthermore, neutralizing antibodies mapping to the carboxyl-terminal intracytoplasmic domain have been generated in guinea pigs (Björling et al. 1991) although the relevance of such antibodies *in vivo* remains uncertain.

Discussion

In general, there is a very strong similarity between the antigenic epitopes of SIV and HIV-2 and given that HIV-2 is closely related to SIV the high degree of antigenic relatedness is perhaps to be expected. Cross reactive linear epitopes have been identified for both viruses which map to the C1 and V2 epitopes in gp120 and to the immunodominant epitope of gp41. A conformation-dependent epitope, recognized by neutralizing antibodies is also common to both viruses. Other neutralizing epitopes shared by SIV and HIV-2 are located in V2 and in gp41 and analogous neutralizing epitopes have been described for HIV-1 (reviewed by Beretta and Dalgleish, 1994; Sattentau and Moore, 1995). For SIV, an additional neutralizing epitope mapping to V4 has been reported whereas for HIV-2 a neutralizing epitope in C3 is not shared with SIV.

The B-cell epitopes of SIV and HIV-2 are broadly similar to those recognized on HIV-1 envelope glycoproteins (reviewed by Beretta and Dalgleish, 1994; Sattentau and Moore, 1995; Moore and Ho, 1995) but with a few notable exceptions. As discussed above, the cysteine loop of SIV, analogous to the V3 region of HIV-1, shows little antigenic variation (Burns and Desrosiers, 1991). The V3 region of HIV-2 is more variable than the same region in SIV, particularly in isolates derived from AIDS patients or from those with a rapid-high phenotype in culture (Korber et al., 1995, Albert et al., 1996). The

differences between aligned amino acid sequences of the HIV-2 V3 loops have been found to range up to 30% non-identity. The differences in HIV-1 V3 loops are even more extreme, ranging up to 60% among M group sequences, and there may be distinctive evolutionary pressures on the V3 loop even among the HIV-1 M group clades (Korber et al., 1994). The difference in the antigenic variation of the V3 regions of SIV, HIV-2 and HIV-1 suggests some functional difference between the V3 regions of these viruses and if neutralization is taken as a marker of biological function this may be the case. Peptides corresponding to the V3 region of T-cell adapted strains of HIV-1 induce neutralizing antibody and early studies suggested that V3 was the principal neutralizing determinant (Javaherian et al. 1989). Indeed, most of the neutralizing activity from experimentally infected or gp120 vaccinated animals was shown to be directed against the V3 region (Matthews et al. 1986; Putney et al. 1986; Robey et al. 1986; Goudsmit et al. 1988; Rusche et al. 1988; LaRosa et al. 1990; Javaherian et al. 1990). More recent studies however, have shown that the V3 region of primary isolates of HIV-1 is poorly exposed and such viruses are much less sensitive to neutralization by antibodies recognising linear V3 epitopes (reviewed by Moore and Ho, 1995). In primary isolates, V3 may be just part of a more complex epitope (Moore and Ho, 1995).

The ability of the V3 region of SIV and HIV-2 gp120 to induce neutralizing antibody is less well defined. While the linear V3 region of SIVmac is unable to induce neutralizing activity (Javaherian et al. 1992, Kent et al. 1992) the V3 region of SIVagm is recognized by a MAb which, under certain conditions, has been shown to neutralize (Allan, personal communication). However, a role for V3 as part of a complex conformation-dependent neutralizing epitope has been defined (Kent et al. 1993) and components of this epitope are shared with HIV-2 (Kent et al. 1993; Robinson, personal communication). For HIV-2, some studies have shown that linear V3 can induce neutralizing antibody (Björling et al. 1991, 1994; Matsushita et al. 1995; McKnight et al. 1996) whereas others have failed to do so (Robert-Guroff et al. 1992; Babas et al. 1994; McKnight et al. 1996; Traincard et al. 1994). The functional role of V3 in SIV and HIV-2 may be more similar to that of primary isolates of HIV-1 than to the role of V3 in highly adapted T-cell tropic strains.

It is notable that the C4 region of both SIV and HIV-2 is less antigenic than the corresponding region of HIV-1. The linear C4 region and the complex CD4 binding site involving the C4 region are highly immunogenic in HIV-1 and the target of neutralizing antibodies able to inhibit the CD4/gp120 interaction (reviewed by Beretta and Dalgleish 1994; Sattentau and Moore, 1995). In contrast, the same regions of SIV and HIV-2 are recognized by sera from infected macaques (McBride et al. 1993, Silvera et al. 1994, Siegel et al. 1992) or infected patients (de Wolf et al. 1991; Norrby et al. 1991) but monoclonal antibodies mapping to linear epitopes have not been described. Only two neutralizing MAbs mapping to a conformation-dependent epitope are reported to inhibit CD4/gp120 interaction (Doyle et al. 1995) but there is no direct evidence to suggest binding of these antibodies to the C4 region or to the CD4 binding site.

The C5 region of HIV-1 is largely inaccessible to antibody binding (Moore et al. 1994) but the carboxyl-terminal portion contains a highly conserved immunodominant epitope that is recognized by patient sera (reviewed by Beretta and Dalgleish, 1994). Likewise, sera from SIV infected macaques or HIV-2 infected patients are able to recognize a C-terminal peptide on the respective envelope glycoproteins.

The similarities between the B-cell epitopes of SIV and HIV-2 are striking and confirm the genetic relatedness of these viruses. The differences between the SIV/HIV-2 group and HIV-1 may indicate functional differences in the envelope glycoproteins and may reflect the tropisms of the viruses. It remains to be seen if the differences in V3 and the C4/CD4 binding site region of SIV/HIV-2 and HIV-1 are indicative of different mechanisms of attachment and entry of virus into target cells.

Table 1 SIV B-cell epitopes located in the envelope glycoproteins

Region	Amino acids	Antibody Identification	Isolate[1]	Specification[2]	Reference
C1	aa21-40	KK3, KK18	SIVmac 32H	Mouse MAb	Kent et al. 1992
C1	aa21-40	Senv71.1	SIVmac BK-28	Mouse MAb	Collignon (Unpublished), D'Souza et al. 1993
C1	aa41-60	KK68	SIVmac J5	Mouse MAb	Kent et al. 1993
C1	aa41-60	-	SIVmac J5	Macaque sera	McBride et al. 1993
C1	aa81-100	KK12	SIVmac 32H (CR)	Mouse MAb	Kent et al. 1992, Mannervik et al. 1992
V1	aa111-130	-	SIVmac 32H	Macaque sera	McBride et al. 1993, Silvera et al. 1994
V1	aa141-160	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
V1	aa141-160	KK65, KK66, KK67	SIVmac 32H	Mouse MAb	Kent et al. 1993
V1/V2	aa8-303	KK8, KK11, KK19, KK21, KK22	SIVmac 32H	Mouse MAb	Kent et al. 1991,1992
V1/V2	aa8-303	Senv 50.1	SIVmac BK-28	Mouse MAb	Collignon (Unpublished), D'Souza et al. 1993
V2	aa161-180	-	SIVmac 32H	Macaque sera	McBride et al. 1993, Silvera et al. 1994
V2	aa161-180	Senv1.1	SIVmac BK-28	Mouse MAb	Collignon (Unpublished), D'Souza et al. 1993
V2	aa166-181	-	SIVmac251	Macaque sera	Torres et al. 1993a
V2	aa167-177	MATG2033	SIVmac251	Mouse MAb	Benichou et al. 1992
V2	aa170-196	-	SIVsm	Macaque sera	Samuelsson et al. 1993
V2	aa171-190	-	SIVmac 32H	Macaque sera	Benichou et al. 1993, Silvera et al. 1994
V2	aa171-190	KK43, KK52	SIVmac 32H (CR-KK52 only)	Mouse MAb	Kent et al. 1992, 1993
V2	aa171-190	KK10, KK13, KK54	SIVmac 32H	Mouse MAb (neut)	Kent et al. 1992, 1993
V2	aa173-185	MATG2014	SIVmac251(CR)	Mouse MAb (neut)	Benichou et al. 1992
V2	aa175-182	M318T	SIVmac251 (CR)	Mouse MAb (neut)	Matsumi et al. 1995
C2	aa221-240	-	SIVmac J5	Macaque sera	McBride et al. 1993
C2/V3	aa294-305 -		SIVmac251	Macaque sera	Torres et al. 1993a

Table 1 (cont) SIV B-cell epitopes located in the envelope glycoproteins

Region	Amino acids	Antibody Identification	Isolate[1]	Specification[2]	Reference
V3	aa311-330	-	SIVmac 32H	Macaque sera	McBride et al. 1993, Benichou et al. 1993, Silvera et al. 1994
V3	aa311-330 aa321-340	KK45	SIVmac 32H	Mouse MAb	Kent et al. 1992
V3	aa313-346	-	SIVsm	Macaque sera	Samuelsson et al. 1993
V3	aa321-340	-	SIVmac 32H	Macaque sera	McBride et al. 1993 Silvera et al. 1994
V3	aa321-340	KK42, KK46	SIVmac 32H	Mouse MAb	Kent et al. 1992
V3		AG1.0	SIVagm	Mouse Mab (neut)	Allan (Unpublished) Kent KA. 1995
V3	aa317-350	-	SIVagm	Green monkey sera	Siegel et al. 1992
V3/C3	aa331-350	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
V4	aa411-430	1B9, 6C11	SIVmac251	Mouse Mab (neut)	Babas et al. 1995
V4	aa414-434	-	SIVmac142	Mouse sera (neut)	Torres et al. 1993a
				Macaque sera	Torres et al. 1993b
V4/C4	aa421-440	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
C5	aa501-520	-	SIVmac32H	Macaque sera	McBride et al. 1993, Silvera et al. 1994
C5	aa514-537	-	SIVsm	Macaque sera	Samuelsson et al. 1993
C5	aa525-538	-	SIVagm	Green monkey sera	Siegel et al. 1992
Conformation-dependent involving V3		KK9	SIVmac 32H	Mouse MAb (neut)	Kent et al. 1993, Choi et al. 1994 Javaherian et al. 1994
Conformation-dependent			SIVmac 32H	Macaque sera	McBride et al. 1993
Conformation-dependent		KK5, KK17, KK57, KK58	SIVmac 32H	Mouse MAb (neut)	Kent et al. 1993, Choi et al. 1994 Javaherian. 1994
Conformation-dependent		Senv7.1, Senv101.1	SIVmac251 BK-28	Mouse MAb (neut)	Collignon (Unpublished), Choi et al. 1994
Conformation-dependent		3C8	SIVmac251	Mouse MAb	Babas et al. 1995
Conformation-dependent		3G8, 3F8, 2.1.13	SIVagm	Mouse MAb	Otteken et al. 1993
Conformation-dependent involving CD4 binding site		KK44, KK56	SIVmac 32H	Mouse MAb (neut)	Kent et al. 1993, Doyle et al. 1995
gp120 unmapped		M56S, M815	SIVmac251	Mouse MAb	Matsumi et al. 1995

Table 1 (cont) SIV B-cell epitopes located in the envelope glycoproteins

Region	Amino acids	Antibody Identification	Isolate[1]	Specification[2]	Reference
gp41	unmapped	KK7	SIVmac 32H (CR)	Mouse MAb	Kent et al. 1992
gp41	unmapped	Senv40.2	SIVmac251 BK-28	Mouse MAb	Collignon (Unpublished)
gp41	aa591-610 aa601-620	KK14, KK15	SIVmac 32H	Mouse MAb	Kent et al. 1992
gp41	aa591-650	-	SIVmac 32H	Macaque sera	Benichou et al. 1993, Silvera et al. 1994
gp41	aa601-620	KK39, KK41, KK53, KK54	SIVmac 32H (CR)	Mouse MAb	Kent et al. 1992
gp41	aa601-620	Senv43.1	SIVmac251 BK-28 (CR)	Mouse MAb	Collignon (Unpublished)
gp41	aa608-638	-	SIVsm	Macaque sera	Samuelsson et al. 1993
gp41	aa621-640	-	SIVagm	Green monkey sera	Siegel et al. 1992
gp41	aa630-634 DWNND	SF8/5E11	SIVmac251	Mouse MAb (neut)	Veronese et al. 1989, Kodama et al. 1991
gp41	aa651-690	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
gp41	aa701-760	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
gp41	aa761-830	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
gp41	aa831-878	-	SIVmac 32H	Macaque sera	Silvera et al. 1994
gp41		2H5, 2.7.15	SIVagm	Mouse MAb	Otteken et al. 1993
gp41		TM105, TM211, TM219, TM30	SIVagm	Mouse MAb	Kodama et al. 1988

[1] CR - antibodies show cross-reactivity with strains of HIV-2
[2] neut - antibodies have neutralizing activity

Table 2 HIV-2 B-cell epitopes located in the envelope glycoproteins

Region	Amino acids	Antibody Identification	Isolate[1]	Specification[2]	Reference
C1	aa30-44, 69-83	-	ISY	Human sera	Mannervik et al. 1992
C1	aa43-53	44.5j	LAV-2/ROD	Rat MAb	McKnight et al. 1996
C1	aa44-56	-	SBL-6669	Human sera	Norrby et al. 1991
C1	aa48-57	125-A	ROD (CR)	Mouse MAb	Traincard et al. 1994
C1	aa83-97	125-H	ROD (CR)	Mouse MAb	Traincard et al. 1994
V1	aa118-125, 125-141	-	ROD	Human sera	deWolf et al. 1991
V1	aa119-137	-	SBL-6669	Guinea pig antisera	Björling et al. 1991
V1	aa125-133	25.8c	LAV-2/ROD	Rat MAb	McKnight et al. 1996
V2	aa140-148	44.5k	LAV-2/ROD	Rat MAb	McKnight et al. 1996
V2	aa149-154	44.2g	LAV-2/ROD (CR)	Rat MAb (neut)	McKnight et al. 1996
V2	aa162-181	125I	ROD (CR)	Mouse MAb	Traincard et al. 1994
V2	aa167-175	44.1b	LAV-2/ROD (CR)	Rat MAb	McKnight et al. 1996
C2	aa196-215	-	ISY	Human sera	Mannervik et al. 1992
C2	aa223-234	44.6i	LAV-2/ROD	Rat MAb	McKnight et al. 1996
C2	aa234-248	-	ISY	Human sera	Mannervik et al. 1992
V3	aa297-330	-	ISY	Human sera	Robert-Guroff et al. 1992, Babas et al. 1994
V3	aa301-315	-	ISY	Human sera	Mannervik et al. 1992
V3	aa303-324	-	ROD	Human sera	deWolf et al. 1991, Norrby et al. 1991
V3	aa304-311	32.2f	LAV-2/ROD	Rat MAb (neut)	McKnight et al. 1996
V3	aa305-320	-	ISY	Human sera	Mannervik et al. 1992
V3	aa306-311	32.7g	LAV-2/ROD	Rat MAb	McKnight et al. 1996
V3	aa310-335	B2C	ROD	Mouse MAb (neut)	Matsushita et al. 1995
V3	aa311-330, 318-337	-	SBL-6669	Guinea pig antisera	Björling et al. 1991
V3	aa311-326, 322-337	3C4	SBL-6669	Mouse MAb (neut)	Björling et al. 1994
V3	aa314-332	125-F	ROD	Human MAb	Traincard et al. 1994
V3	aa318-334	-	ISY	Human sera	Mannervik et al. 1992
V3	aa332-355	-	ISY	Human sera	Mannervik et al. 1992

Table 2 cont HIV-2 B-cell epitopes located in the envelope glycoproteins

Region	Amino acids	Antibody Identification	Isolate[1]	Specification[2]	Reference
C3	aa340-358	-	ROD	Human sera	deWolf et al. 1991
C3	aa366-392	2HIB, 2F19C	ROD	Mouse MAb (neut)	Matsushita et al. 1995
V4	aa398-416	-	ISY	Human sera	Mannervik et al. 1992
C4	aa436-452	-	ROD	Human sera	deWolf et al. 1991, Norrby et al. 1991
C-terminal	aa472-493, 489-509	-	SBL-6669	Guinea pig antisera (neut)	Björling et al. 1991
C-terminal	aa481-498	-	ISY	Human sera	Mannervik et al. 1992
C-terminal	aa486-507	-	ROD	Human sera	deWolf et al. 1991
Conformation-dependent		B23, 17A, 110C	Human primary isolate (CR)	Human MAb (neut)	Robinson(Unpublished), Kent et al. 1993
Conformation-dependent		28.3e	LAV-2/ROD	Rat MAb	McKnight et al. 1996
Conformation-dependent		28.8e	LAV-2/ROD	Rat MAb (neut)	McKnight et al. 1996
Conformation-dependent		25.3f	LAV-2/ROD	Rat MAb	McKnight et al. 1996
gp125 unmapped		125-B, -C, -D, -E, -G	ROD	Mouse MAb	Traincard et al. 1994
gp36	aa573-595	-	SBL-6669	Human sera	Norrby et al. 1991
gp36	aa578-603	36-A, -B, -C	ROD (CR-36-C only)	Mouse MAb	Traincard et al. 1994
gp36	aa595-614	-	SBL-6669	Human sera	Norrby et al. 1991
gp36	aa634-649	-	SBL-6669	Human sera	Norrby et al. 1991
gp36	aa714-729	-	SBL-6669	Guinea pig antisera (neut)	Björling et al. 1991

[1] CR - antibodies show cross-reactivity with strains of SIV
[2] neut - antibodies have neutralizing activity

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